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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,378	WALKLEY, STEVEN	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/042,527.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the Application filed 14 July 2003 as a continuation in part of application 10/042,527, which is a continuation of PCT/GB00/01560. The instant application is also filed as continuation of PCT/US02/000813, which claims benefit of US provisional application 60/347,233 filed 10 January 2002 and claims benefit of foreign applications UK 9909066.4 filed 20 April 1999 and UK 0100889.5 filed 12 January 2001.

The preliminary amendment filed 19 December 2003 has been entered. Claims 1-20 were originally filed. Claims 1-20 were canceled and claims 21-35 were added in the 19 December amendment. Claims 21-35 are presently under consideration.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

The instant application does not name an inventor named on either the 10/042,527 application or the PCT/GB00/01560 as required for benefit under 35 USC §120.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to application 9909066.4. The certified copy has been filed in parent Application No., 10/042,527 filed on 19 October 2001. However, it is noted that the foreign application does not name an inventor in common with the instant application.

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the United Kingdom on 12 January 2001. It is noted, however, that applicant has not filed a certified copy of the 0100889.5 application as required by 35 U.S.C. 119(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-24, 27-31, 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

In the instant case, claims 21-24, 27-31 and 34 encompass a method for treating a mucopolysaccharide disease or reducing neuronal glycolipid storage comprising administering "an inhibitor of glucosylceramide synthesis". Claim 35 is directed to a method of treating a mucopolysaccharide disease in a patient comprising administering an agent capable of increasing

the rate of neuronal glycolipid degradation. As the method claimed requires administration of the inhibitor or an agent capable of increasing the rate of neuronal glycolipid degradation and the outcome recited in the claim is provided by the inhibitor or agent, the inhibitor of glycolipid synthesis and agent capable of increasing the rate of neuronal glycolipid degradation is a critical element of the claimed method.

The Revised Interim Guidelines state, "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (Column 3, page 71434).

Inhibitors of gucosylceramide synthesis are contemplated, *inter alia*: at paragraph 48 of the specification which defines "inhibitor" of glucosylceramide synthesis as including molecules such as N-butyldeoxynojirimycin or N-butyldeoxygalctonojirimycin, PDMP and structural analogs thereof; at paragraph 49 which further contemplates gene-based inhibitors such as antisense sequences or catalytic RNAs; at paragraphs 71-72 which contemplate peptide or protein inhibitors of glucosylceramide synthesis; at paragraph 82, which contemplates antibody inhibitors of glucosylceramide synthesis enzymes; and at paragraph 96 which contemplates triple helix as well as ribozyme inhibitors. In sum, the specification indicates that the glucosylceramide synthesis inhibitor of the claims encompasses any molecule that provides the recited outcome (*i.e.*, inhibitor of any enzyme by any means). However, aside from imino sugar inhibitors of glucosylceramide synthase such as N-butyldeoxynojirimycin or N-butyldeoxygalctonojirimycin, inhibitors of glucosylceramide synthesis are not conventional in the art. In particular, the art does not disclose peptide, antibody, antisense, ribozyme or siRNA inhibitors of glycosylceramide synthesis.

In paragraph 17, the specification teaches that an agent capable of increasing the rate of glycolipid degradation can be an enzyme involved in glycolipid degradation or a molecule which increases the activity of a glycolipid-degrading enzyme. Although the art, like the instant application, contemplates the use of enzyme replacement therapy or bone marrow transplantation in the treatment of some mucopolysaccharidoses, Shiffman *et al.* (2002) *Drugs* 62:733-742 teaches that these approaches are not effective in treating neuronal manifestations of the diseases. Shiffman *et al.* teaches, "Although systemic improvement is likely to be possible with ERT [enzyme replacement therapy] in these diseases, no effect on their neurological manifestations is anticipated" (paragraph bridging the left and right column on page 738) and "effects of BMT [bone marrow transplantation] may be seen in mucopolysaccharidosis type I or II, but again, no effect was seen on the neurological progression" (second full paragraph on in the right column on page 738). With regard to molecules which increase the activity of a glycolipid-degrading enzyme, the art is silent. Thus, the art does not recognize agents that increase the rate of neuronal glycolipid degradation as conventional in the art

The Guidelines for Written Description state: "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" (Federal Register, Vol. 66, No. 4, Column 3, page 1106). "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation

between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" (MPEP §2163(3)(a)(ii)).

In the instant case, the specification provides a detailed description reduction to practice of imino sugar compounds capable of inhibiting glucosylceramide synthase (*i.e.*, NB-DNJ; see especially paragraph 48 and the Examples). The specification does not describe small molecule inhibitors of enzymes involved in synthesis of glucosylceramide synthesis other than glucosylceramide synthase inhibitors and provides only generic prophetic teachings describing how one might identify nucleic acid or polypeptide inhibitors of glucosylceramide synthesis. The specification fails to teach the chemical or physical structures of inhibitors of enzymes other than inhibitors of glucosylceramide synthase. Furthermore, the disclosure fails to teach the relevant identifying characteristics of glucoceramide synthase inhibitors other than imino sugar-structured inhibitors such as NB-DNJ. In particular, neither the art nor the specification disclose a single example of a peptide or nucleic acid-structured inhibitor of glucosylceramide synthesis. Likewise, the specification does not disclose the identity of small molecules capable of increasing the rate of a glycolipid degrading enzyme or enzymes that can be administered to increase the rate of neuronal glycolipid degradation in a mucopolysaccharidosis patient.

The generic teachings of how one might identify inhibitors of glucosylceramide synthesis or agents that increase the rate of neuronal glycolipid degradation found throughout the specification are not a sufficient substitute for an actual description of the molecules used in the method. An adequate written description of an inhibitor of glucosylceramide synthesis or agent that increase the rate of neuronal glycolipid degradation requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a

description of the inhibitor or agent itself. It is not sufficient to define an inhibitor or agent solely by its principal biological property because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any molecule with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all molecules that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d.1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Likewise, adequate description of the methods first requires an adequate description of the materials, *i.e.*, specific inhibitor molecules or agents that increase the rate of neuronal glycolipid degradation, which provide the means for practicing the invention.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of any inhibitor of glucosylceramide synthesis. Therefore, only the described imino sugar-based glucosylceramide synthase inhibitors meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 21-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention: The claims are directed to methods of treating mucopolysaccharide disease in a patient comprising administering a therapeutically effective amount of an inhibitor of glucoceramide synthesis or an agent capable of increasing the rate of neuronal glycolipid degradation. Claims are also directed to methods of reducing neuronal glycolipid storage in mucopolysaccharide disease comprising administering a therapeutically effective amount of an inhibitor of glucosylceramide synthesis.

Breadth of the claims: It is first noted that the instant specification defines "treatment" as "the administration of medicine or the performance of medical procedures with respect to a patient, for either prophylaxis (prevention) or to cure the infirmity or malady in the instance where the patient is afflicted" and paragraph 52 defines "therapeutically effective amount" as "an amount of a reagent sufficient to achieve the desired treatment effect." Thus, construed in light of the specification, the claims are directed to methods of preventing or curing mucopolysaccharidosis or methods comprising administering an amount of an agent in an amount sufficient to obtain prevention or cure in a patient having mucopolysaccharide disease.

Furthermore, the claims encompass methods of preventing or curing any mucopolysaccharide disease including Hurler Syndrome, Hunter Syndrome, Sanfilippo A-D, Morquio A, Morquio B, Maroteaux-Lamy and Sly Syndrome, comprising administering any inhibitors of glucosylceramide synthesis or any agent capable of increasing the rate of neuronal glycolipid degradation. It is also noted that it is clear from the discussion of delivery options contemplated for the invention that the claims encompass gene therapy and antisense therapy as a mode of treatment (see especially paragraphs 71-108).

State and level of predictability in the art: First, with regard to gene therapy in general, at the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin et al. further states in a report to the NIH that, "... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene

therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

In more recent article, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remain unsolved at the time the application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical**

hurdles to be overcome in the future", beginning on page 116 and continued through page 125).

Next, with regard to antisense or inhibitory RNAs, although the prior art teaches that antisense RNA and ribozymes can be used to suppress gene expression, these methods require detailed knowledge of the target molecule and empirical experimentation to identify an effective inhibitory molecule. Far et al. (*Bioinformatics* (2001) 17:1058-1061) teach that the "successful use of [antisense oligonucleotides] to suppress gene expression is somewhat limited since only a small portion of all possible antisense species against a given target sequence shows efficacy..." (page 1058, column 1, first paragraph of the introduction). Far also teaches that in spite of a considerable amount of empirical data on the use of antisense oligonucleotides, the work "does not seem to be reflected by the knowledge on the biophysical and biochemical level of the action of [antisense oligonucleotides] nor by the knowledge about the rules that govern the relationship between specific sequences of [antisense oligonucleotides], the influence of the target structure, the annealing *in vitro*, and the efficacy *in vivo"* (beginning on page 1058, column 1, third from final line through the fourth line of column 2). Finally, Far teaches, "the effectiveness of [antisense oligonucleotides] is strongly dependent on local target RNA structures, on chemical properties and sequences of the [antisense oligonucleotide] species, and on the characteristics of the biological system of interest including the metabolic properties of the target RNA and the gene product, respectively" (page 1058, column 2, first full paragraph).

A recent article by Braasch *et al.* (*Biochem.* (2002) 41:4503-4510) emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has

been suggested that many published studies are at least partially unreliable" (page 4503, first and second paragraphs). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (page 4503, first and second paragraphs). Branch (1998) *Trends Biochem. Sci.* 23:45-50 (made of record in the IDS filed 29 July 1999) adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:3161-3163 (made of record in the IDS filed 29 July 2003) teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (page 3161, second and third columns).

Braasch *et al.* discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that

obscure effects due to the intended antisense mechanism" (page 4503, paragraphs 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm *et al.* (2001) *Lancet* 358:489-497 states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

With regard to preventing or curing, mucopolysaccharide diseases, Schiffmann *et al.* (*supra*) teaches that, although there are reports of some success in alleviating peripheral effects using enzyme replacement therapy or bone marrow transplantation in some forms of mucopolysaccharidosis, there is no evidence of prevention or cure in these patients. Shiffman *et al.* teaches, "Thus far, only one non-blind trial has been published of the use of ERT [enzyme replacement therapy] in 10 patients with mucopolysaccharidosis type I, which is caused by a deficiency of the alpha-L-iduronidase...This nonblind trial suggested that recombinant human alpha-L-iduronidase may be useful for a number of non-CNS manifestations of mucopolysaccharidosis type I" (left column on page 738). Shiffman *et al.* further teaches, "BMT [bone marrow transplantation] has more limited effect in the other disorders [other than type I Gaucher disease]. BMT stabilized or slightly improved the general condition, cardiomyopathy and facial features, but skeletal benefit was limited.[] The authors of this study concluded that BMT can prolong life and improve its quality in well-chosen patients. Benefit was seen also in cell therapy using cord blood from an affected matched brother with Marteaux-Lamy disease with improvement of quality of life, facial features and joint mobility. Similar effects of BMT

may be seen in mucopolysaccharidosis type I or II, but again, no effect was seen on the neurological progression" (second full paragraph in the left column on page 738; citations omitted). Thus, although the art recognizes some symptomatic relief provided by enzyme replacement therapy or bone marrow transplantation in certain types of mucopolysaccharidoses, these approaches are not effective in treating neurological manifestations of the diseases and are far from constituting preventions or cures.

Finally, with regard to therapy using small molecule enzyme inhibitors of glucosylceramide synthase such as NB-DNJ, Shiffman *et al.* teaches that although there have been some initial successes in treating type I Gaucher disease, "The ultimate usefulness of this treatment approach cannot be assessed at this early stage" (third full paragraph on page 739). Thus, Shiffman *et al.* clearly teaches that all modes of therapy for mucopolysaccharidoses are at an early stage of development and there is no evidence of a treatment approach that is enabled to prevent or cure any mucopolysaccharidosis. In particular, Shiffman *et al.* teaches that the therapeutic efficacy of substrate deprivation by inhibition of glucosylceramide synthesis remained to be established at the time the instant application was filed.

Still further, even if an effective therapy were available for any given mucopolysaccharidosis, the art recognizes that mucopolysaccharidoses are a heterogeneous group of diseases. For example, Muenzer *et al.* (2004) *J. Pediatrics* 144:S27-S34 teaches, "Clinical presentation, severity of symptoms, and central nervous system involvement can vary widely both within and between the seven major types, distinguished by the specific enzyme deficiency, the major clinical features or both" (fifth paragraph on page S27; see also Table I, which shows the variety of enzyme deficiencies and glycosaminoglycan abnormalities leading to

the various types of mucopolysaccharidoses). Thus, evidence of a therapeutic effect in any one type of mucopolysaccharidosis is not evidence of general enablement for prevention or cure of the broad scope of mucopolysaccharide disease.

Amount of direction provided by the inventor and existence of working examples: In the working examples, Applicant demonstrates that a mouse model of MPS IIIA (Sanfilippo disease) treated with NB-DNJ exhibited a reduction in GM2 ganglioside in the brain (Example 3 and Figures 2-5). However, although the specification teaches that the MPS IIIA mice exhibit a variety of phenotypic characteristics of the disease including decreased activity, scruffy coat, abdominal distention, hunched posture, waddling gait, severe ataxia, tremors and weight loss, the specification does not disclose the effects of treatment on any of these symptoms such that it can be determined whether the method results in prevention or cure and there is no evidence of record to indicate that a reduction in GM2 ganglioside in the brain is recognized as a surrogate end point for prevention or cure of MPS IIIA. Importantly, the specification teaches in paragraph 12, "In addition to GAG storage, other materials may accumulate in MPS-affected tissues as well. For example, glycolipid accumulation has been reported in central nervous tissue of man and animals with a variety of MPS diseases []. The precise relationship between the effects of the primary storage material, GAGs, and these other materials on the observed disease pathologies is uncertain" (emphasis added). This teaching clearly suggests that changes in GM2 ganglioside in the brain of an MPS IIIA mouse cannot be taken as evidence of an effective therapy without some evidence correlating that endpoint with therapeutic outcome.

With regard to practicing the claimed methods beyond the scope of administering NB-DNJ, the specification merely provides teachings such as, "In one embodiment, a nucleic acid

comprising a sequence encoding a peptide or protein inhibitor of glucosylceramide synthesis is administered. In another embodiment, a nucleic acid sequence encoding an agent capable of increasing the rate of neuronal glycolipid degradation, *e.g.* a glucosylceramide glucosidase, is administered" (paragraph 71) and general teachings of how to administer peptides and nucleic acids. However, there is no specific disclosure of which peptides, nucleic acids and small molecules actually possess the properties of inhibitors of glucosylceramide synthesis or agents capable of increasing the rate of neuronal glycolipid degradation. Furthermore, there is no guidance in the specification would address the general unpredictability of establishing effective therapies using nucleic acid or peptide inhibitors of glucosylceramide synthesis or agents capable of increasing the rate of neuronal glycolipid degradation.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, the ordinary skilled artisan would not be able to make or use the invention as claimed without undue experimentation. The art recognizes a high degree of unpredictability in obtaining success using the methods of the instant Application. The reason for this unpredictability stems first from the lack of guidance as to how to make and use inhibitors of glucosylceramide synthesis other than imino sugar-based glucosylceramid synthase inhibitors, or how to use *any* agent administered by gene therapy; the lack of direction in the art with regard to how to effectively treat any mucopolysaccharidosis, particularly the neurological manifestations thereof, by administering an inhibitor of glucosylceramide synthesis or increasing the rate of neuronal glycolipid degradation; and the art recognized heterogeneity of mucopolysaccharidoses. Furthermore, this unpredictability is

compounded by the fact that, as Applicant states, "There is as yet no accepted treatment for any of the MPS diseases" (paragraph 13).

The teachings of the specification remedy deficiencies in the art only with respect to demonstrating a decrease in GM2-gaglioside in the brains of MPS IIIA mice; however, based on Applicant's own teachings, the validity of this model as an indicator of therapeutic outcome is unclear. Given the high degree of unpredictability in the art, the skilled artisan would have to engage in undue experimentation to extend the teachings of the specification in order to establish any effective treatment, prevention or cure for any mucopolysaccharidosis. Therefore, the claims are properly rejected under 35 U.S.C. §112, first paragraph, as lacking enablement.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M Sullivan, Ph.D.
Examiner
Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER